Remarks

Amendments to the Claims

The amendments to claim 1 do not add new matter. The amendments to part (a) of claim 1 are supported, for example, on page 17, lines 8-20. The amendments to part (b) of claim 1 are supported by claim 1 as originally filed.

Status of the Claims

The Office Action indicates that claims 55-59, 88, and 89 are withdrawn. Applicants understand that method claims 55-59 may be rejoined at the close of prosecution. However, Applicants object to the withdrawal of claims 88 and 89.

In the paragraph bridging pages 2 and 3, the Examiner states that claims 88 and 89 were withdrawn because they "are drawn to a modified or mutant form of a TCR bound phage" which allegedly is not encompassed by claim 1. This is an improper characterization of the scope of claim 1. Claim 1 recites "an interchain disulfide bond." The claim does not specify whether the bond is the native bond or an introduced bond. Therefore claim 1 compasses displayed TCRs which are either natural (only applicable of course to heterodimeric TCRs) or "mutated" or "modified" by the introduction of an artificial interchain bond (applicable to both dimeric and single chain TCRs). Hence claims 88 and 89, which specify non-natural, introduced interchain bonds, are properly dependent on claim 1. Applicants note that withdrawal of claims 88 and 89 is inconsistent with the examination of claims 86 and 87, which also relate to mutated TCRs.

Information Disclosure Statement

The PTO Form 1449 returned with the Office Action indicates that none of the references listed are in the PTO's file. WO 99/018129 and Weidanz *et al.*, *J. Immunol. Methods 221*, 59-76 were cited in the rejections below, and US 2002/058253 is available from the PTO's own records. A new Form 1449 and copies of the other listed references accompany this paper. Please return an initialed copy of the Form 1449 with the next Office Action.

Rejection Under 35 U.S.C. § 101

Claims 1, 6, and 86-89 stand rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter. Applicants respectfully traverse the rejection.

The Office Action contends that the recited phage particle "would read on a naturally occurring phage particle which displays on its surface a dimer of T-cell receptor i.e., alpha beta TCR" and cites Xu[1] to support this contention. Paragraph bridging pages 3 and 4 of the Office Action. As an initial matter, Xu discusses inter alia the similarities and differences between the variable domains of antibodies and TCRs, especially in terms of their CDRs. This paper contains no reference to the phage display of TCRs and only a single mention of phage-displayed antibody libraries (last paragraph of left column of page 42).

Claims 1, 6, and 86-89 do not read on naturally occurring phage particles. Naturally occurring phage particles do not display T cell receptors on their surface. A phage (otherwise known as a bacteriophage) is a virus that only infects bacterial cells (prokaryotes). TCRs are produced only by eukaryotes. In order for a naturally occurring phage particle to display on its

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[1] Xu *et al.*, *Immunity 13*, 37-45, 2000, at page 37, col. 1.

surface a dimeric TCR, the phage particle would have to have incorporated into its genome the DNA encoding both a TCR alpha chain and a TCR beta chain. The DNA encoding each of the TCR chains is present on different chromosomes in humans (chromosome 14 for TCR alpha chains and chromosome 7 for beta chains), and the DNA encoding each domain of the TCR chains is not contiguous. Furthermore, the TCR chain-encoding DNA would have to encode soluble portions of both the TCR alpha chain and TCR beta chain. The probability of any naturally occurring phage particle having separately acquired all the component DNA sequences required to present a TCR on its surface can safely be ignored.

Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1

Claims 86 and 87 stand rejected as allegedly containing new matter which is not described in the specification. The Office Action contends that the specification does not support the recitation "interchain disulfide bond has no equivalent in native T cell receptors." Office Action at page 5, last paragraph. Applicants respectfully traverse the rejection.

The recitation of an interchain disulfide bond which has no equivalent in native T cell receptors is supported throughout the specification. For example, page 13, lines 5-13 (emphasis added) teaches:

> (iv) the proteinaceous particle is a phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a scTCR polypeptide comprising TCR amino acid sequences corresponding to extracellular constant and variable domain sequences present in native TCR chains and a linker sequence, the latter linking a variable domain sequence corresponding to that of one chain of a native TCR to a constant domain sequence corresponding to a constant domain sequence of another native TCR chain, and **a**

disulfide bond which has no equivalent in native T cell receptors links residues of the constant domain sequences.

Page 15, lines 16-31 (emphasis added) teaches:

> The displayed scTCR polypeptide may be, for example, one which has
>
> > a first segment constituted by an amino acid sequence corresponding to a TCR α or δ chain variable domain sequence fused to the N terminus of an amino acid sequence corresponding to a TCRa chain constant domain extracellular sequence,
> >
> > a second segment constituted by an amino acid sequence corresponding to a TCRss β or γ chain variable domain fused to the N terminus of an amino acid sequence corresponding to TCR β chain constant domain extracellular sequence,
> >
> > a linker sequence linking the C terminus of the first segment to the N terminus of the second segment, or vice versa, and
> >
> > a disulfide bond between the first and second chains, **said disulfide bond being one which has no equivalent in native αβ or γδ T cell receptors**.

Page 17, lines 8-20 (emphasis added) teaches:

> The dTCR which is displayed on the proteinaceous particle may be one which is constituted by
>
> > a first polypeptide wherein a sequence corresponding to a TCR a or 8 chain variable region sequence is fused to the N terminus of a sequence corresponding to a TCRa chain constant domain extracellular sequence, and
> >
> > a second polypeptide wherein a sequence corresponding to a TCRα or β chain variable domain sequence fused to the N terminus a sequence corresponding to a TCRα chain constant domain extracellular sequence,

> the first and second polypeptides being linked **by a disulfide bond which has no equivalent in native αβ or γδ T cell receptors**.

Page 22, lines 1-8 (emphasis added) teaches:

> A principle characterising feature of the preferred dTCRs and scTCRs displayed by proteinaceous particles of the present invention, is a disulfide bond between the constant domain extracellular sequences of the dTCR polypeptide pair or first and second segments of the scTCR polypeptide. That bond may correspond to the native inter-chain disulfide bond present in native dimericass TCRs, or **may have no counterpart in native TCRs**, being between cysteines specifically incorporated into the constant domain extracellular sequences of dTCR polypeptide pair or first and second segments of the scTCR polypeptide.

The specification amply supports recitation of an interchain disulfide bond which has no equivalent in native T cell receptors. Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 86 and 87 stand rejected under 35 U.S.C. § 112 ¶ 2 as indefinite. The Office Action contends that the recitation "no equivalent" is not clear, "especially in the absence of positive support in the specification." Office Action at page 5, last paragraph. Applicants respectfully traverse the rejection.

It is well settled that, under 35 U.S.C. § 112 ¶ 2, a claim must "reasonably apprise those skilled in the art both of the utilization and scope of the invention." *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 136, 118 U.S.P.Q. 122, 130 (2d Cir. 1958), *cert. denied*, 358 U.S. 884 (1958). Claims 86 and 87 meet this standard.

The position of the unique native inter-chain disulfide bond of TCRs is well known; this bond extends between residue 4 encoded by Exon 2 of the TRAC*01 gene, and residue 2 encoded by Exon 2 of the TRBC*01 or TRBC*02 gene. See pages 77 and 188 of the

international ImMunoGeneTics database (IMGT) reference book, The T Cell Receptor Facts Book, referenced on page 3 lines 8 to 9 of the specification and provided with the accompanying IDS. The IMGT nomenclature (TRAC*01 etc.) used is clear, is in widespread use by those working in the T-cell receptor field, and is explained in The T Cell Receptor Facts Book. Copies of pages 76-78 (which relate to the TRAC constant domain gene) and pages 188-191 (which relate to the TRBC1 and TRBC2 TCR constant domain genes) are provided with the accompanying IDS, and the residues connected by the bond are indicated.[2]

The constant region α and constant region β sequences present in any construct can be mapped to the constant region α and constant region β of native TCRs; if the bond is in any position other than the position of the naturally occurring disulfide bond, then clearly it is one which "has no equivalent in native TCRs."

Claims 86 and 87 are definite. Please withdraw the rejection.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 6, 86, and 87 stand rejected under 35 U.S.C. § 102(b) as anticipated by Weidanz I (*J. Immunol. Methods*), Weidanz II (WO 99/18129), and Nissim (WO 01/62908). Applicants respectfully traverse the rejections.

A reference cited under 35 U.S.C. § 102 must expressly or inherently describe each element set forth in the rejected claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d

[2] These pages use the full TRAC*01/TRBC1*01/TRBC2*01 nomenclature, as used in the present application, to specify the individual allele of each gene to which reference is being made. Note that there are two alleles listed for each of the TRBC1 and TRBC2 genes and each allele pair encodes the same amino acid sequence; however, proper use of the nomenclature ideally specifies the particular allele used as the reference point. It is for this reason that the specification refers to a particular allele in all cases, *e.g.*, TRAC, TRBC1 and TRBC2. The "*01" portion of the nomenclature is in this particular case redundant but not ambiguous.

628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). None of the cited references meets this standard.

Weidanz I

Weidanz I does not disclose all the features of the phage particle recited in claim 1. First, all the phage-displayed TCRs disclosed in Weidanz I are single-chain TCRs containing at most three domains (Vα-linker-VβCβ). See Figures 1a and 1b on page 66, which illustrate the two and three domain single-chain TCR constructs discussed in this paper. See also the Abstract on page 59, especially lines 4-5.[3] Section 2.3 on page 61, "Construction of scTCR fusions," explains that "[t]he Vα and VβCβ domains were linked together by a $(G_4S)_4$ peptide linker." The final paragraph of that section makes it clear that the phage-displayed anti-p53 TCR construct contained the first seven N-terminus amino acids of the Cα domain (APEPNQI) fused to the C-terminus of the Vα domain in the three domain scTCR construct utilized.

Moreover, the phage-displayed single-chain TCR constructs in Weidanz I disclosed do no contain an interchain disulfide bond within the TCR portion thereof of any description. See page 65, section 3.1, final paragraph, which explains that the phage-displayed scTCR constructs disclosed were "truncated at the amino acid just prior to the final cysteine." This truncation removes the cysteine residue from the TCR β chain that is involved in forming the interchain disulfide bond in native TCRs.

On page 61, section 2.3, right column Weidanz I explains that the phage-displayed scTCR constructs disclosed either contained no part of the Cα domain, or only the seven N-terminus amino acids of the Cα domain (APEPNQI) fused to the C-terminus of the Vα domain in the three domain scTCr construct utilized. These seven N-terminus amino acids at the amino acid present

[3] Weidanz I mentions a (hetero)dimeric TCR construct (page 60, right column, first paragraph); however, this comment is in relation to the native TCR, not the phage-displayed TCR construct generated from it.

in this portion of the wild-type Cα domain and are not capable of forming a disulfide interchain bond with the Cβ constant domain. The cysteine residue from the TCR α chain that is involved in forming the interchain disulfide bond in native TCRs occurs near the C-terminus of the extracellular portion of the Cα domain and is therefore not present in any of the disclosed phage-displayed scTCR constructs.

The examiner asserts that claims 86 and 87, which recite a disulfide bond, would be inherent to the TCR dimer which is formed by the disulfide bonds between alpha and beta TCR chains. However, claims 86 and 87 additionally specify that the recited interchain disulfide bonds must not correspond to the interchain disulfide bonds found in native TCRs.

Weidanz II

Weidanz II also lacks disclosure of a construct as claimed in the present application in this document (*i.e.* a phage particle displaying on its surface a single chain or dimeric T cell receptor comprising an interchain disulfide bond linking residues of constant domain sequences). The two and three domain scTCR constructs disclosed in Weidanz I are also disclosed in Weidanz II, which contains the following disclosure (on page 15, lines 15-29; emphasis added) relating to the length of the TCR constant domain sequence that may be included in such three domain TCR constructs:

> The V-α chain of the sc-TCR molecule can further include a C-β chain or fragment thereof fused to the C-terminus of the V-β chain. Further, the V-α chain can include a C-α chain or fragment thereof fused to the C terminus of the V-α chain and the N-terminus of the peptide linker sequence. **Generally, in those fusion proteins including a C-β chain fragment, the fragment will have a length of approximately 50 to 126 amino acids and will usually not include the last cysteine residue at position 127. For those fusion proteins comprising a C-α chain, the length can vary between approximately 1 to 90 amino acids (ie. the C-α chain up to but not including the final cysteine).** For example,

> in one embodiment, the fusion protein includes a C-α chain fragment between about 1 to 72 amino acids starting from amino acid 1 to 72. In another embodiment, the C-α chain fragment is between about 1 to 22 amino acids starting from the first amino acid to 22 (leucine). **The C-α chain fragment typically does not include any cysteine resides except the $C_{\alpha 90}$ variant which includes two cys residues.**

The absence of cysteines according to the above directions of course excludes the possibility of an interchain bond between residues in the constant regions.

Moreover, in all three Weidanz II fragments, the Cα chain fragment ended at a cysteine residue. This "final" cysteine was changed to a serine residue but no internal cysteines were mutated. Final construct pKC73 has 22 amino acids of the C-α chain, pKC74 has 72 amino acids, and pKC75 has 90 amino acids (*i.e.*, the entire C-α chain). See Figure 9A, which schematically represents the pKC73, pKC74 and pKC75 DNA vector inserts. None of these inserts contains a disulfide interchain bond in the their constant regions.

Nissim

The examiner asserts that Nissim discloses "a phage-display, comprising recombinant phages each of which codes for a T-cell receptor (TCR) recognition element, and/or a mutation and variant, in which the vector expresses a recombinant TCR recognition element from each of the recombinant phages" and that this is sufficient to anticipate claims 1, 6, 86, and 87. However, claim 1 recites a disulfide interchain bond between constant domain residues. Nissim does not disclose this element of the invention.

On page 9, lines 1-25 (emphasis added), Nissim teaches:

> In one embodiment the TCR recognition element comprises a variable fragment of the TCR, mutant and variant thereof. The variable fragment includes but is not limited to: one or more of TCR variable α (TCRVα), TCR variable β (TCRVβ), TCR variable γ (TCRVγ), or TCR variable δ (TCRVδ) domains. In another

> embodiment the variable TCR variable a (TCRVα), TCR variable β (TCRVβ), TCR variable γ (TCRVy), or TCR variable δ (TCRVδ) domains comprises one or more of the CDR1, CDR2 or CDR3 segments. In another embodiment the TCR recognition element comprises **a** constant fragment. **The** constant fragment of the TCR includes but is not limited to Cα, Cβ1, Cβ2, Cγ or Cδ.
>
> Such phage displayed reagents include but are not limited to the following: a single chain TCRVα/TCRVα, a single chain TCRVβ/TCRVβ, a single chain TCRVy/TCRVy, a single chain TCRVδ/TCRVδ, a single chain TCRVα/TCRVβ, a single chain TCRVα/TCRVy, a single chain TCRVα/TCRVδ, a single chain TCRVβ/TCRVα, a single chain TCRVβ/TCRVy, a single chain TCRVβ/TCRVδ, a single chain TCRVγ/TCRVα, a single chain TCRVγ/TCRVβ, a single chain TCRVγ/TCRVδ, a single chain TCRVδ/TCRVα, a single chainTCRVδ/TCRV, a single chain TCRVδ/TCRVy and/or a mutation and variant thereof.

These disclosures make it clear that Nissim contemplates three-domain scTCR constructs that comprise only one TCR constant domain. Such constructs cannot comprise a disulfide interchain bond between constant domain residues as recited in claim 1.

None of the cited references teaches each element of independent claim 1 or dependent claims 6, 87, and 88. Please withdraw the rejections.

Respectfully submitted,

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